Provisional chapter

The Imaging of Inflammatory Bowel Disease: Current Concepts and Future Directions

Rahul A. Sheth and Michael S. Gee

Additional information is available at the end of the chapter

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1. Introduction

Radiologic techniques play an integral role in the diagnosis and management of patients with inflammatory bowel disease (IBD). Imaging has long been utilized to evaluate segments of the digestive tract that are inaccessible to conventional endoscopy. While endoscopy offers unparalleled visualization of the large bowel lumen and biopsy capabilities, the small bowel remains essentially wholly inaccessible by conventional endoscopic techniques [1]. Thus, one important role that imaging plays in the care of patients with IBD is the evaluation of the small bowel.

With the advancement of cross-sectional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI), the role of imaging in IBD has greatly expanded to include the mucosal, transmural, extraluminal, and extra-intestinal manifestations of these diseases. Imaging now not only assists in making the diagnosis of IBD, including helping to discriminate between ulcerative colitis and Crohn's disease, but also is a critical component in the determination of active versus indolent disease. Imaging assessment of IBD activity is increasingly being utilized by surgeons and gastroenterologists for treatment planning and as a biomarker of treatment response/resistance. Urgent and emergent complications of IBD including abscesses, fistulae, perforations, obstructing strictures, and toxic megacolon are also best detected by cross-sectional imaging techniques over endoscopic methods [2]. Imaging is pivotal in the identification of extra-intestinal involvement of IBD, processes that both provide important adjunctive data in the diagnosis of IBD as well as contribute significantly to the morbidity and mortality of IBD. Techniques such as MRI that provide superior soft tissue contrast allow for both the improved visualization of the perianal disease manifestations of Crohn's disease such as fistulae and abscesses, as well as the precise anatomic localization for treatment planning [3]. Moreover, as our understanding of the pathophysiologic underpinnings of IBD continually expands, novel molecular imaging approaches have been applied to

highlight the specific intra-cellular perturbations occurring within the bowel and thus identify areas of pathology with unparalleled resolution and specificity.

Multiple radiologic modalities, including fluoroscopy, CT, MRI, ultrasound, and nuclear medicine/molecular imaging techniques, have been applied towards imaging IBD. In this chapter, we will discuss technical considerations, appropriate indications, and key imaging findings for the most common imaging modalities currently applied in the care of patients with IBD. We will also discuss the risks attendant to the use of ionizing radiation, imaging findings of the extra-intestinal manifestations of IBD, and the potential role that molecular imaging may play in the future for patients with IBD.

2. Fluoroscopic imaging

2.1. Indications

Fluoroscopic imaging historically has been considered as the "gold standard" approach to imaging the small bowel. Despite the promotion of newer endoscopic technologies such as video capsule endoscopy and double balloon endoscopy, as well as the development of cross-sectional methods such as CT and MR enterography, fluoroscopy remains a staple tool for the identification of small bowel pathology, particularly pathology involving the terminal ileum. The benefits of fluoroscopic imaging include the ability to visualize peristaltic loops of small bowel in real time, a feature that allows for the discrimination between true abnormalities and transient changes in configuration related to motion. Additionally, with optimal contrast opacification, inspection of the mucosal surface of the entire length of the small bowel in relief is feasible. The examination may be performed as either a small bowel follow through, in which oral contrast is administered, or as a small bowel enteroclysis, in which the patient undergoes nasojejunal intubation followed by catheter instillation of both positive and negative contrast agents at a controlled rate. Advantages of the latter include more uniform distention and opacification of the entire small bowel leading to enhanced detection of segmental strictures and mucosal disease from double contrast opacification. Enteroclysis is particularly useful in patients with intermittent symptoms of IBD, as the complete distention of the small bowel can provoke correlative imaging findings which may otherwise go undetected with a standard oral contrast preparation in a small bowel follow through. Significant disadvantages of enteroclysis are invasiveness and patient discomfort. Though fluoroscopic examination of the small bowel is still widely used, trans- and extramural disease are poorly detected with this technique. Moreover, the exposure of patients to ionizing radiation with this modality should be taken into consideration, particularly in patients who are likely to undergo frequent imaging examinations.

2.2. Technical considerations

In fluoroscopic imaging, conventional two-dimensional radiographs are obtained with the patient lying on an examination table. The patient is kept nil per os (NPO) for several hours prior to the examination; a bowel cleansing regimen is rarely employed. Bowel visualization

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is achieved following the administration of radio-opaque contrast agents, a large class of solutions that generally contain varying concentrations of barium. The benefits of fluoroscopic imaging include the ability to visualize peristaltic loops of small bowel in real time, a feature that allows for the discrimination between true abnormalities and transient changes in configuration related to motion. Additionally, with optimal contrast opacification, inspection of the mucosal surface along the entire length of the small bowel in relief is feasible. The patient's position can be adjusted by the fluoroscopist to any desirable obliquity with respect to the X-ray source so that the outline of every loop of small bowel is visualized. The fluoroscopist also employs compressive maneuvers using paddles, balloons, and gloves to spread out the loops of bowel so that they are individually visible.

In a small bowel follow through, the patient is asked to drink approximately 500cc of a barium containing oral contrast solution. Serial spot radiographs are obtained until the bolus has passed the terminal ileum into the cecum; this takes approximately 45-60 minutes, though pro-peristaltic agents such as metoclopramide may be administered to accelerate the process. Fluoroscopy with compression is then performed to identify areas of pathology.

In enteroclysis, a naso-jejunal catheter is placed such that the tip of the catheter terminates in the proximal jejunum, distal to the ligament of Treitz. A barium-containing solution is then infused at a uniform rate through the catheter. One variation is to infuse methylcellulose after a small amount of barium; this "double contrast" technique offers an improved inspection of the mucosal surface pattern [4]. Advantages of naso-jejunal intubation include bypassing the regulatory mechanisms of the pylorus and a more uniform distention and opacification of the entire small bowel, particularly in patients who are unable to drink an adequate volume of contrast by their own volition. Enteroclysis is particularly effective in provoking radiographic evidence of low-grade partial obstructions in patients with intermittent symptoms, findings that may have been undetectable by small bowel follow through. The process of naso-jejunal intubation and infusion of contrast, however, can be very uncomfortable, and in some cases intolerable, for patients; some institutions provide conscious sedation for that reason.

2.3. Interpretation of imaging findings

Much of the fluoroscopic imaging of UC, which predominantly involves the large bowel, has been replaced by colonoscopy. However, approximately 20% of patients with severe UC have associated "backwash" ileitis. Fluoroscopy demonstrates a patulous, incompetent ileocecal valve with a granulated mucosal relief pattern of the terminal ileum. This finding is in contrast to Crohn's disease, which is characterized by a stenotic ileocecal valve with luminal narrowing and ulceration of the terminal ileum. Backwash ileitis usually resolves following total colectomy [5].

Crohn's disease can affect the digestive tract anywhere from the mouth to the anus; approximately 80% of these patients have small bowel involvement (Figure 1). Unlike UC, "skip areas" of uninvolved bowel may be interspersed between segments of affected bowel. However, Crohn's disease has a predilection for affecting the terminal ileum. The earliest radiographic sign of Crohn's disease is aphthous ulcers, which appear as shallow collections of

contrast with surrounding radiolucent haloes due to adjacent mucosal edema. Aphthous ulcers are not specific to Crohn's disease and may be seen in a number of diseases. However, as Crohn's disease progresses, the ulcers coalesce to form linear, curvilinear, or spiculated areas of ulceration along the mesenteric border of the small bowel. There is resultant retraction of the bowel wall, leading to pseudodiverticula and pseudosacculation of the anti-mesenteric bowel wall. These active inflammatory changes can lead to intermittent small bowel obstruction, which is best diagnosed by enteroclysis technique. Severe disease produces a classic "cobblestone" appearance, with deep transverse and longitudinal ulcerations bordered by areas of edema creating a checkered mucosal relief pattern. Chronic Crohn's disease leads to circumferential bowel wall thickening and irreversible stricture formation.

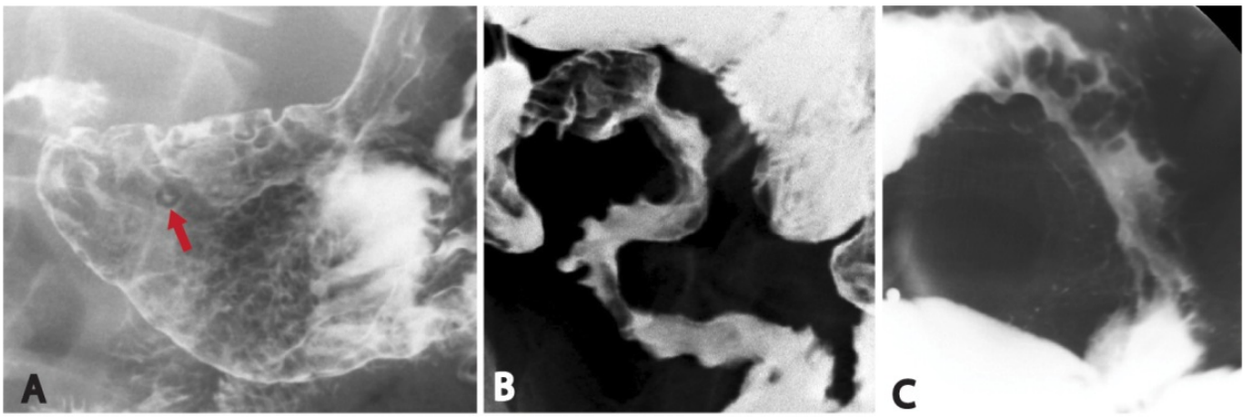

Figure 1. Fluoroscopic imaging findings in Crohn's disease. A, Aphthous ulcers, which appear as focal collections of contrast with surrounding haloes of mucosal edema, are present in early Crohn's disease (red arrow). B, Progressive disease results in longitudinal ulcerations on the mesenteric bowel surface with pseudosacculation formation on the anti-mesenteric surface. C, Severe disease can have a "cobblestone" mucosal relief pattern due to intersecting transverse and longitudinal ulcers.

Though fluoroscopic examination of the small bowel is still widely used, trans- and extramural disease are poorly detected with this technique. Moreover, the exposure of patients to ionizing radiation with this modality should be taken into consideration, particularly in patients who are likely to undergo frequent imaging examinations.

3. Computed tomographic imaging

3.1. Indications

Computed tomography remains the work-horse imaging modality for IBD and its complications in the United States. As a high-resolution cross-sectional technique, CT can visualize not only the bowel lumen, but also the bowel wall, visceral fat, intra-abdominal lymph nodes, and mesenteric vasculature supplying the bowel. Extraintestinal disease manifestations such as nephrolithiasis, sacroiliitis, and primary sclerosing cholangitis can readily be evaluated. Computed tomography can additionally be performed rapidly, and CT scanners are

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present in most emergency rooms, rendering it an ideal choice in the urgent or emergent setting. As such, CT is an appropriate imaging examination for the diagnosis of IBD, the evaluation of response to intervention including post-surgical changes, and the detection of urgent and emergent complications such as abscess formation and acute bowel obstruction. However, since subtle mucosal ulcerations are not well visualized by CT, this modality should not be used as a first line approach for the detection of suspected mild disease.

3.2. Technical considerations

The past two decades have witnessed a revolution in the technology of CT scanners. The introduction of the helical CT scanner has permitted the acquisition of volumetric data sets in a continuous, uninterrupted manner. The source data are obtained with sub-millimeter slice thickness, so that images may be be reconstructed from the source axial plane into standard coronal or sagittal planes, or any other plane desired by the radiologist. Also, the advent of multidetector row scanners, initially with 4-slice devices in 1998, followed by 8-, 16-, 64-, and most recently 320-slice devices, has had a dramatic effect on reducing scanning time. This, in turn, has shortened the requisite breath hold for the patient, making the examination more comfortable and less often degraded by respiratory motion artifact [6].

There exist a variety of CT protocols for abdominal indications. With regards to IBD, a common reason to pursue imaging is for the assessment of small bowel pathology. CT enterography is usually the imaging protocol of choice, which combines large volume enteral contrast distention of small bowel with intravenous contrast administration. For this imaging examination, patients are kept NPO for several hours prior; similar to fluoroscopy, a bowel cleansing regimen is not routinely required. Intravenous contrast is always used when possible. Enteral contrast is an indispensible component of the technique. Initial CT enterography relied on “positive” enteral contrast agents, usually barium containing solutions whose higher attenuation characteristics opacify the bowel lumen. However, differentiating the thin line of mucosal enhancement due to intravenous contrast from the opaque enteral contrast in the bowel lumen can be challenging. Therefore, a more popular approach is to use “neutral” enteral contrast agents that distend but do not opacify the bowel lumen. In this manner, mucosal enhancement patterns are better seen, as are areas of non-distensibility such as strictures. Water is a commonly used neutral enteral agent, but since this has the disadvantage of being absorbed by the body, commercially available preparations that are isodense to water on CT imaging but are non-absorbable are also prevalent [7]. Essentially all current CT enterography protocols utilize neutral enteral contrast.

The volume of enteral contrast administered to the patient and the duration over which they are asked to ingest contrast vary by institution. However, the overall goal is to maximize uniform distention of the small bowel, which typically requires 1000-1500 mL of contrast. Patients are first instructed to drink the enteral contrast, generally over approximately 45 to 60 minutes. They then lie down on the CT scanner; intravenous contrast is administered; originally CT enterography studies were scanned at 55-60 seconds post-contrast (enterographic phase) coinciding with peak superior mesenteric artery enhancement. However,

many institutions now perform scanning during portal venous phase (~70 seconds) for optimal visceral organ evaluation.

The CT analog to fluoroscopic enteroclysis, known at CT enteroclysis, is also used as a method to achieve optimal luminal filling. A naso-jejunal tube is required and is usually inserted in a fluoroscopy suite. Contrast is administered under fluoroscopic guidance, after which the patient is transported to the CT scanner. Unlike fluoroscopy, though, a real-time assessment of bowel distensibility cannot be made by CT, as the patients are usually only imaged after the contrast has been fully administered. The disadvantage of patient discomfort caused by naso-jejunal intubation is no different.

For patients suspected of bowel obstruction or perforation, oral contrast is frequently contraindicated and traditional CT imaging with IV contrast only is recommended.

An important concern with CT is the use of ionizing radiation. Recent studies suggest that CT exams account for the vast majority of ionizing radiation exposure to IBD patients from imaging, especially among patients diagnosed at an early age. An informed analysis of the associated risks, especially for the pediatric patient, should be performed prior to each examination.

3.3. Interpretation of imaging findings – Crohn's disease

A principal clinical question for which CT is utilized in IBD is the determination of active versus inactive disease in the small bowel. This distinction is of high clinical significance: patients with active inflammation are treated medically with immuno-modulatory therapy, while symptomatic patients with inactive, fibrosed strictures often require surgical intervention. Areas of actively inflamed bowel on CT most commonly demonstrate pathologic bowel thickening, which is defined as bowel wall greater than 3mm in thickness. A 3mm cutoff was selected by consensus as the best compromise between sensitivity and specificity and is for the most part used universally for all cross-sectional modalities including MRI and ultrasound. Another differentiating characteristic of active disease is mucosal hyperenhancement, which appears as a pencil-thin line outlining the luminal surface of the bowel wall and reflects the hyperemia of inflammation (Figure 2A). This finding is considered the most sensitive for active disease, and the degree of hyperenhancement may correlate with the degree of underlying inflammation. Active inflammation also results in submucosal edema, which manifests on CT examination as a lower attenuation submucosal layer interposed between mucosal and serosal layers. This mural stratification is also referred to as the "target sign" due to its characteristic appearance (Figure 2C). The most specific feature for active Crohn's disease is engorgement of the vasa recta adjacent to an inflamed loop of bowel, a finding known as the "comb sign" (Figure 2B). Secondary signs for active inflammation include mesenteric fat stranding, focal ascites adjacent to bowel, and lymphadenopathy. Of note, while mucosal hyperenhancement and abnormal bowel thickening are frequent features of active Crohn's disease, they are not specific and may be seen in infectious enteritis or mesenteric ischemia. Similarly, mural stratification can be seen in UC as well as bowel ischemia. On the other hand, the "comb sign" is considered fairly specific for Crohn's disease [2, 7].

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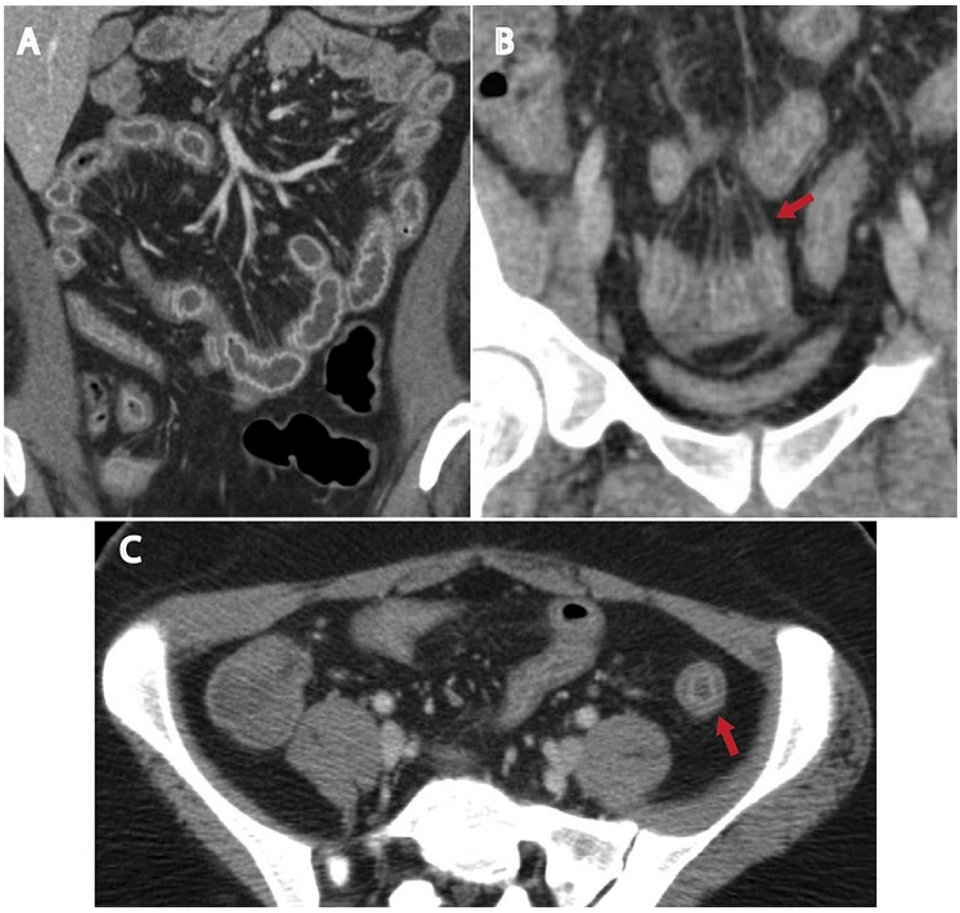

Figure 2. CT findings in acute Crohn's disease. A, Active inflammation causes mucosal hyperenhancement and bowel wall thickening greater than 3mm. B, Engorgement of the vasa recta adjacent to an inflamed loop of bowel is a specific finding in active Crohn's disease and has been coined the "comb sign." C, Submucosal edema yields a characteristic "target sign."

The presence of mucosal hyperenhancement, abnormal bowel wall thickening, mural stratification, and prominent adjacent vasa recta in an area of poorly distensible bowel suggests that the stricture is due to active inflammation and is thus potentially reversible by medical interventions. The strictures of chronic Crohn's disease, in contrast, are fibrotic, irreversible, and do not demonstrate the features of active disease described above. The presence of luminal narrowing with proximal bowel dilation is suggestive of fibrosis. Long-standing inflammation leads to fat deposition within the submucosa of the bowel wall; this apparent mural stratification should not be confused with the "target sign" of active disease and can be differentiated based on the Hounsfield attenuation characteristics of fat, which is less than 0 Housfield units (Figure 3A). Secondly, the fibrotic retraction preferentially affects the mesenteric bowel wall, leading to the pseudosacculation appearance on the anti-mesenteric side that can also be seen by fluoroscopy. Finally, chronic transmural Crohn's disease, possibly due to chronic inflammatory stimulation, produces a fibrofatty proliferation of the mesenteric fat, also known on CT examinations as the "creeping fat sign" (Figure 3B).

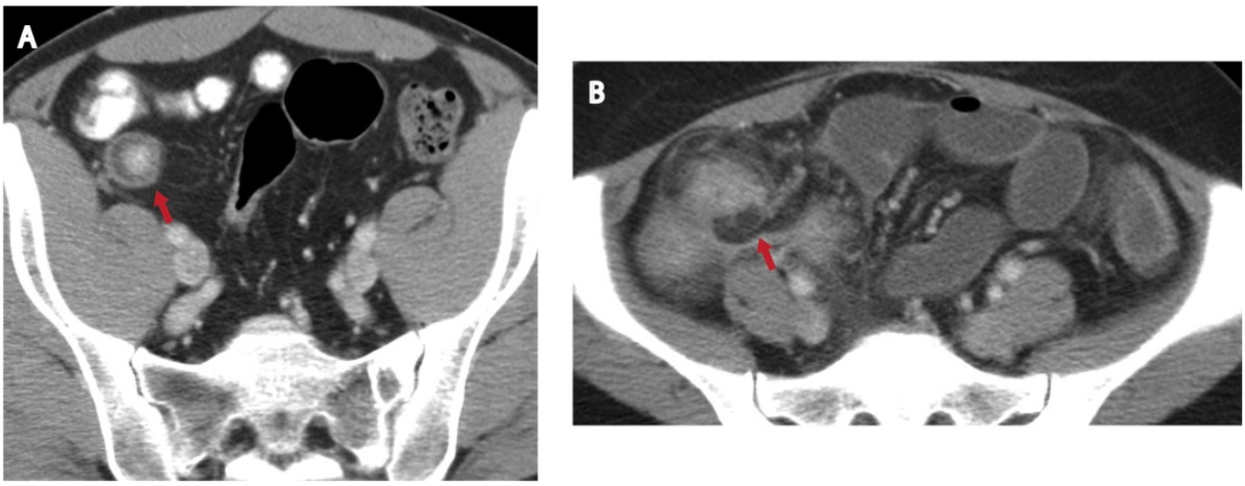

Figure 3. CT findings in chronic Crohn's disease. A, Fatty depositions in the submucosal layer may mimic the "target sign" of active disease (red arrow). B, Fibrofatty proliferation of the mesenteric fat, or "creeping fat," (red arrow) is seen in chronic, transmural disease.

The extra-mural complications of Crohn's disease are excellently depicted by CT. Penetrating disease is present in approximately 20% with Crohn's disease, with fistulas representing the most common pathology in this category [3]. Fistulous tracts may form between any two epithelially lined viscera in the abdomen, such as other loops of bowel (entero-enteric), the bladder (entero-vesicular), and the skin (entero-cutaneous). A communicating tract that fills with enteral contrast is diagnostic (Figure 4A). Evaluation with CT is highly sensitive for the detection of fistulae, though certain anatomic locations such as the perianal region are better imaged by MRI, as discussed below.

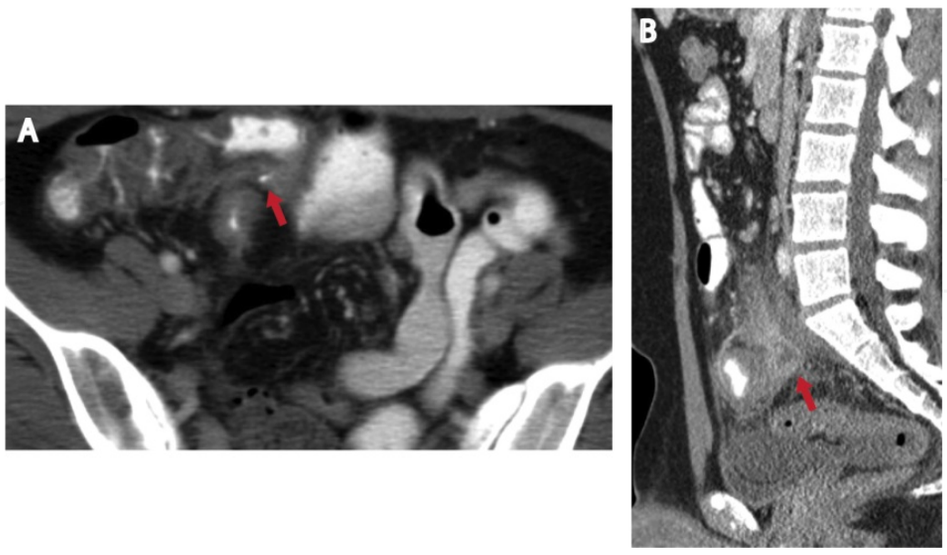

Figure 4. Complications of Crohn's disease on CT. A, A fistula between two loops of small bowel is well depicted by CT as a thin tract of oral contrast connecting the lumens of the two loops. B, An intra-abdominal abscess posterior to the distal large bowel, likely due to a microperforation, was identified in this patient.

Intra-abdominal abscesses are extra-luminal fluid collections that do not communicate with the bowel (Figure 4B). The discontinuity of the abscess collection with the bowel lumen is important to verify but can occasionally be challenging, as neural enteral contrast within the bowel mimics the attenuation characteristics of the infected fluid within the abscess cavity. For this reason, positive enteral contrast is often preferred to neutral contrast in patients with suspected abscess.

3.4. Interpretation of imaging findings – Ulcerative colitis

As discussed previously, colonoscopy remains the primary approach for diagnosing and determining extent of disease in UC. However, severe complications of UC such as toxic megacolon are an important indication for imaging, with CT representing the mainstay modality in these unstable patients. CT findings include thinning of the colonic wall, luminal distension, and pneumatosis; severe cases can lead to perforation and free intraperitoneal gas.

4. Magnetic resonance imaging

4.1. Indications

Magnetic resonance imaging enjoys many inherent advantages over other cross-sectional imaging modalities. These include the ability to acquire images in any imaging plane, the lack of ionizing radiation, and excellent soft tissue resolution. Because of the lack of ionizing radiation, imaging may be performed at multiple time points during an examination, for example at different phases of contrast enhancement, providing a multiparametric assessment of any particular pathology. Additionally, "cine" images can be obtained sequentially over time, in an MRI analog to fluoroscopy.

The strengths of MRI when applied towards IBD are best suited for investigating the small bowel and the perianal region, anatomic locations towards which Crohn's disease demonstrates a tropism. Magnetic resonance imaging of the large bowel, an examination that would have increased relevance in UC, is not routinely performed. The intrinsic spatial resolution of MRI is inferior to that of CT. An MRI examination also takes longer to complete than a CT exam. However, the widespread adoption of new, faster MRI pulse sequences, described in the subsequent section, has significantly reduced scanning time and opened the door for small bowel imaging. For specific clinical scenarios, such as perianal disease, MRI is the recognized gold standard non-invasive technique.

4.2. Technical considerations

As with CT, multiple different MRI protocols exist for examining the abdomen. In the realm of IBD, one very useful MR examination is magnetic resonance enterography (MRE). Although an in-depth discussion of the various pulse sequences used in abdominal MRI imaging is beyond the scope of this text, a familiarity with the commonly used sequences is valuable in understanding the applicability of MRE. Sequences with T2 weighting are the

best for evaluating the bowel wall. Intravenous contrast enhancement appears bright on T1 weighted sequences; however, as feces can occasionally be bright on T1 imaging too, pre-contrast T1 image sets are obtained to help identify true enhancement. Conventional spin echo pulse sequences do not afford the requisite temporal resolution to image the abdomen during a single breath hold; as such, the resulting images are often degraded by respiratory motion artifact. Beyond that, high temporal resolution is made all the more critical when investigating a moving target as the bowel. For these reasons, MRE capitalizes on customized MR pulse sequences that offer improved temporal resolution and are able to image the entire abdomen during a single breath hold. For example, single-shot turbo spin echo (e.g. SSFSE or HASTE) sequences produce high quality, motion-free T2 weighted images of the entire bowel [8]. Balanced steady state free precession sequences (e.g. FIESTA or TrueFISP) are T1 and T2 intermediate-weighted sequences that that are rapid and demonstrate increased conspicuity of the mesentery for detection of inflammatory changes or fistula formation [9]. These sequences, due to their rapidity, can be performed as thick slab cinematic acquisitions to evaluate bowel peristalsis, known as MR fluoroscopy. Fat suppression is routinely employed during both T2-weighted and T1-weighted post-contrast sequences, to highlight areas of bowel wall edema and enhancement. The post-contrast T1 fat-suppressed sequences are performed using 3-D techniques to accelerate image acquisition and enable dynamic evaluation of bowel enhancement at multiple timepoints post-contrast. An average imaging time for MRE, exclusive of the time required for enteral contrast administration, is approximately 30-45 minutes.

Diffusion weighted imaging (DWI) is an MRI technique that has been used with tremendous success in neurological imaging and has shown promise in gastrointestinal imaging. Diffusion imaging provides quantitative maps of the ability of water molecules in tissue to randomly move in a process known as Brownian motion. In areas of inflammation, hypercellularity, or ischemia, the free movement of water molecules is restricted; this characteristic manifests as a low apparent diffusion coefficient (ADC) value when MRI sequences sensitive to diffusion are obtained. Diffusion weighted imaging is at present an experimental technique in IBD imaging (Figure 5), but initial reports have suggested that this method may not only improve disease detection but also provide a quantitative metric for assessing interval changes in bowel wall inflammation [10].

There is no specific bowel preparation prior to MRE, but patients generally are kept NPO for several hours prior to the exam. Anti-peristaltic agents such as glucagon may help improve image quality and are often administered just prior to imaging. Intravenous contrast with a gadolinium-chelate containing agent is standardly administered. There are several options in enteral contrast, which can be categorized by their MRI signal characteristics. “Negative” agents are intrinsically T1 and T2 dark compounds that usually contain superparamagnetic iron oxide particles. Their principal advantage is that they emphasize mucosal enhancement and bowel wall edema. “Positive” agents are intrinsically T1 and T2 bright compounds; these, similar to positive CT contrast agents, may obscure mucosal enhancement findings and thus are infrequently used. The most commonly used class of MR enteral contrast agents is the “biphasic” type, which are T1 dark and T2 bright (e.g. dilute barium with sorbi-

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tol, polyethylene glycol). With these agents, one can readily assess the pattern of bowel wall folds on T2 weighted images without losing mucosal enhancement data on T1 weighted images [11]. Contrast agents are often hyperosmolar to maximize luminal distention; an important side effect for patients to be aware of is diarrhea. It is critically important that patients ingest adequate enteric contrast for MR enterography. Unlike CT in which underdistended bowel loops can still be evaluated, the relative diminished spatial resolution of MRI renders collapsed bowel difficult to assess for disease. In addition, enteric contrast is needed to displace intraluminal air that can produce significant susceptibility artifact on dynamic post-contrast MRI sequences.

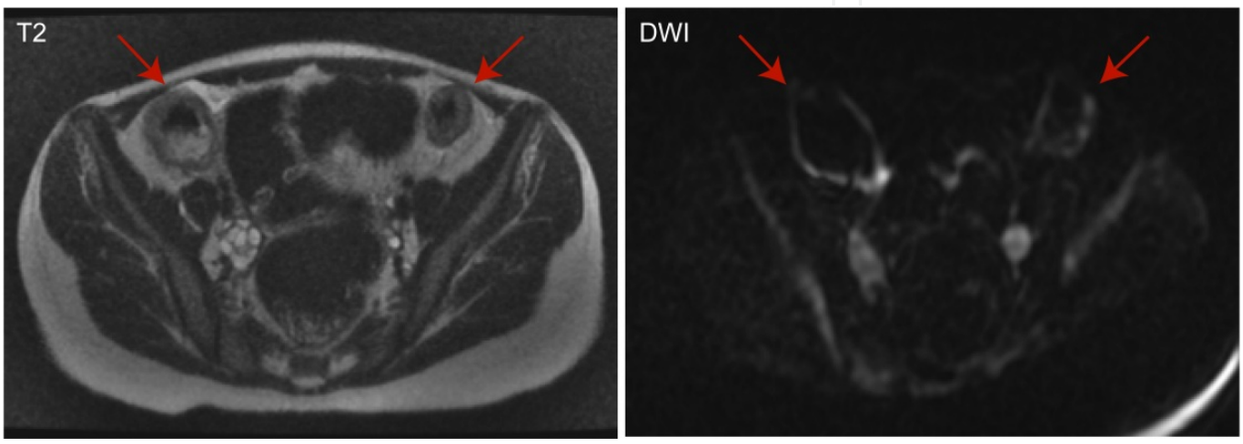

Figure 5. Representative T2 (left) and diffusion weighted (right) images from an MR enterography of a child with Crohn's disease. Images demonstrate two colonic loops (red arrows) exhibiting bowel edema and restricted water diffusion, consistent with active inflammation.

Enteral contrast is primarily administered orally, though MR enteroclysis is also an option. The attendant patient discomfort and added radiation from the fluoroscopy-guided placement of the naso-jejunal tube are identical to the CT analog. However, one benefit of MR enteroclysis is the ability to perform MR fluoroscopy during the instillation of enteral contrast, a technique that provides dynamic information regarding bowel distensibility.

Patients may be imaged in the supine or prone position; the latter orientation is preferred at some institutions as the patient's own weight is used to spread out loops of small bowel; the compression in the anterior-posterior dimension also reduces imaging volume.

4.3. Interpretation of imaging findings – Crohn's disease

Magnetic resonance imaging is an excellent tool for the detection of active Crohn's disease, with a sensitivity of > 90% [12]. Many of the imaging characteristics of active Crohn's disease on MRI, as one may expect, are morphologically identical to those appreciated on CT. For example, bowel wall thickening greater than 3mm is considered abnormal and evidence of active inflammation. Active disease with intramural edema manifests as T2 hyperintensity between the mucosa and muscularis propria (Figure 6A) [13]. Mucosal hyperenhancement is also an important marker of active disease. Diffuse, avid, homogeneous mucosal

enhancement is suggestive of active disease (Figure 6B). Alternatively, low-level, heterogeneous mural enhancement without a mucosal component with upstream dilatation favors the diagnosis of mural fibrosis due to irreversible collagen deposition in the bowel wall (Figure 6C). Ulceration may be difficult to identify without proper bowel distention; ulcers appear as thin lines of high signal intensity within thickening loops of bowel. Both MRI and CT are insensitive for early aphthous ulcers, for which fluoroscopy or endoscopy should be considered as more sensitive.

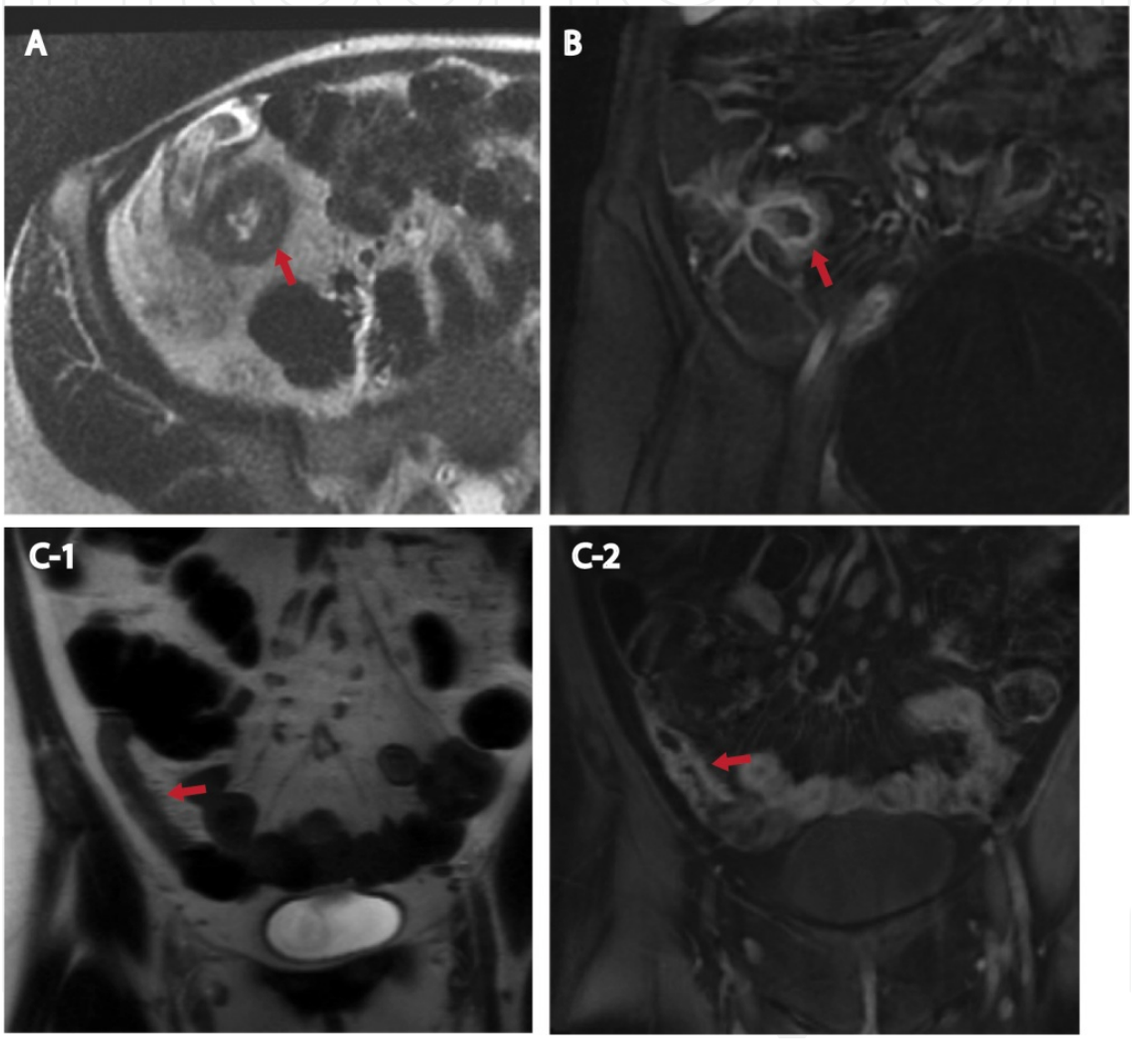

Figure 6. Findings of Crohn's disease by MR enterography. A) Submucosal edema appears as T2 hyperintensity interposed between the mucosa and muscularis propria (red arrow). B) Homogeneous, avid mucosal enhancement on T1-weighted imaging is suggestive of active disease (red arrow). C) Conversely, fixed lumimal narrowing on a T2 weighted image (red arrow, C-1) that demonstrates delayed mural enhancement on a post contrast T1 weighted image (red arrow, C-2) without a mucosal component is seen in chronic fibrosis.

Additional evidence of active disease such as the "comb sign," in which there is engorgement of the mesenteric vessels adjacent to an inflamed loop of bowel, are well identified by MRI. Strictures appear as a focal narrowing in the bowel lumen and are considered signifi-

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cant if there is a pre-stenotic dilation of the proximal bowel. The so-called "creeping fat sign" occurs in chronic, transmural inflammation, in which hypertrophy of the mesenteric fat produces mass effect and surrounds viscera; this sign is specific for Crohn's disease. Another sign of chronic fibrosis is T2 hypointensity of the bowel wall relative to muscle.

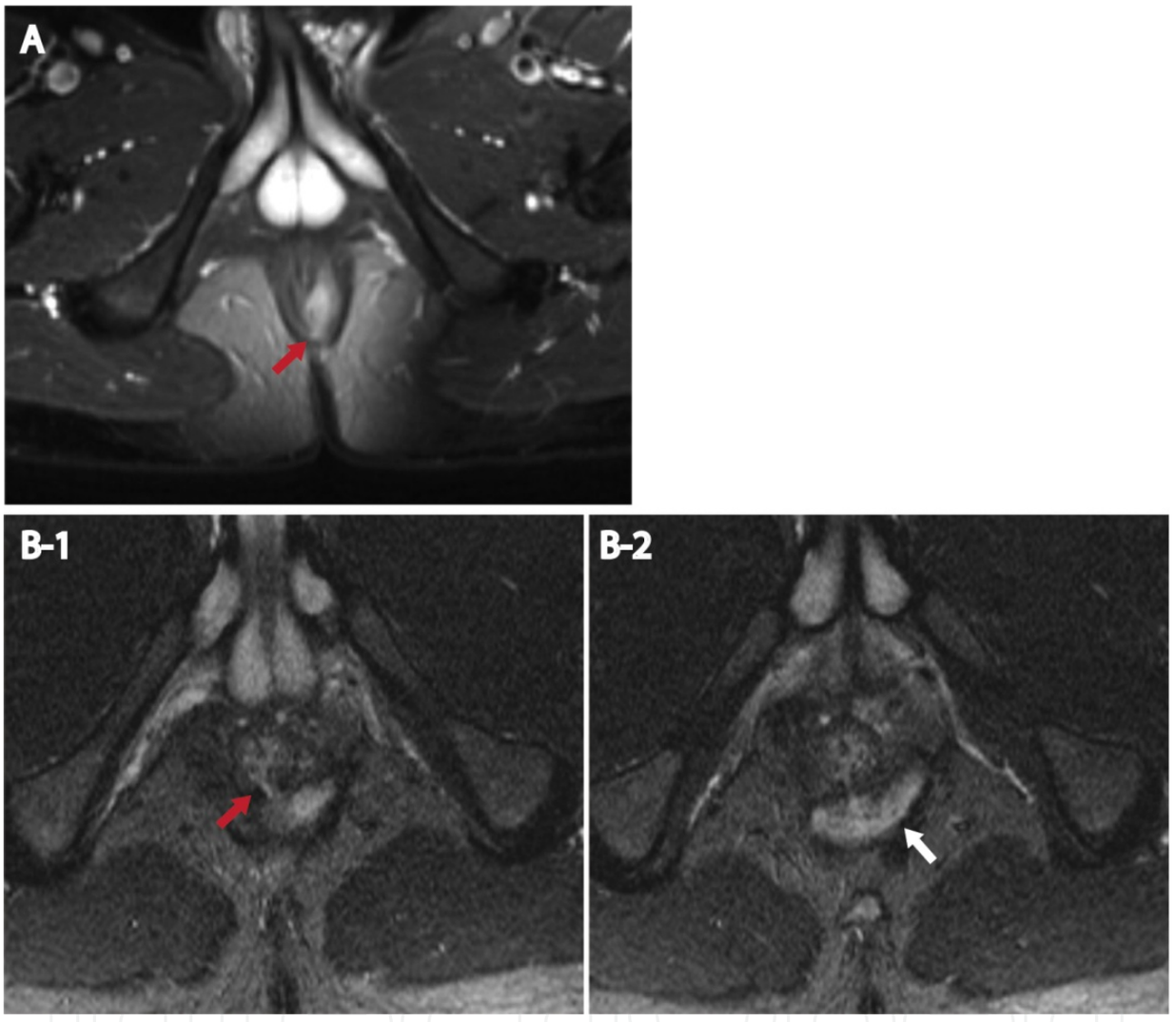

Figure 7. MRI findings of anorectal fistulae. A, T2 hyperintensity that extends between the external and internal sphincter complexes is diagnostic of an intersphincteric fistula (red arrow). B, Two sequential T2 weighted images demonstrate a linear hyperintense focus traversing through the internal and external sphincter complexes consist with a transsphincteric fistula (red arrow, B-1). The subsequent image demonstrates an associated fluid collection extending into the left ischioanal fossa (white arrow, B-2).

Extramural disease is as conspicuous, if not more so, on MRI as it is on CT. Fistulae appear as T2 hyperintense tracts that avidly enhance and extend from bowel to a second epithelial lined organ such as another segment of bowel, the skin, or the bladder. Sinuses are blind-ending tracts that extend from bowel and typically terminate within the mesentery. Both fistulae and sinuses cause translocation of gut flora out of the bowel and can be associated with abscess formation.

In addition to evaluating the small bowel with enterography, MRI is a powerful tool in the investigation of perianal Crohn's disease because of its superior soft tissue contrast for delineation of the anal sphincter complex. The lifetime risk of developing fistulous disease in Crohn's disease is approximately 20-40%. Anorectal fistulae are common and are classified based on their location relative to the anal sphincter complex and pelvic floor musculature, as anatomic location impacts upon treatment options. The most common type of anorectal fistula is the intersphincteric fistula (Figure 7A), followed by the transphincteric fistula (Figure 7B). The accuracy of MRI for diagnosing and classifying anorectal fistulae is comparable to exam under anesthesia [3].

5. Ultrasound

5.1. Indications

Ultrasound is a cross-sectional imaging technique that has been used extensively in the imaging of IBD. As with other technologies, ultrasound has its own unique set of advantages, such as low relative cost, lack of ionizing radiation, and real-time imaging capability. Disadvantages include the inability to visualize portions of small bowel, rectum, and sigmoid, difficulty tracing long bowel segments, as well as operator dependence, with the quality of the examination contingent on the technical skill of the ultrasonographer. Ultrasound has been shown to possibly be as accurate in the diagnosis of IBD as CT and MRI based on detection of wall thickening and hypervascularity by Doppler. However, a high sensitivity is likely achievable only in the hands of an expert ultrasonographer, a resource that is not widely available or easy to standardize. Ultrasound is particularly relevant in pediatric imaging: the smaller body habitus in this patient population allows for a more complete examination, and the lack of ionizing radiation is likely safer compared to CT. The most common indication for ultrasound is evaluation for active inflammation in a symptomatic IBD patient whose anatomic distribution of bowel inflammation is known.

5.2. Technical considerations

Similar to the previously described modalities, minimal patient preparation is required in ultrasound. Since luminal gas can cause acoustic shadowing artifacts that obscure underlying structures, non-effervescent liquid may be administered to displace bowel gas distally and provide some luminal distension. The choice of ultrasound transducer is predicated by the patient's body size. Higher frequency transducers produce higher resolution images but have poorer tissue penetration compared to lower frequency transducers. Practically, an ultrasonographer will begin the examination with the highest frequency transducer available, which is usually a 15 megahertz transducer; if there are structures that are not well seen, the ultrasonographer change to a lower frequency one.

The approach to handling the ultrasound transducer and physically tracing it across the abdomen is of paramount importance. A key technique in imaging the bowel is known as "graded compression." Increasing pressure is applied with the transducer head as it is

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swept across the surface of the abdomen. This has the effect of displacing bowel gas and overlying bowel loops so that the area of interest can be inspected with the greatest possible clarity [14].

5.3. Interpretation of imaging findings

A normal segment of bowel on ultrasound exhibits five discrete layers. The inner-most layer is a thin hyperechoic line that demarcates the interface between the lumen and the mucosa. The next layer is a hypoechoic line at the interface between the mucosa and submucosa. The third layer is a hyperechoic line between submucosa and the muscularis propria; this is the most commonly involved layer in IBD. The fourth layer is the muscularis propria itself and is hypoechoic. The fifth and final layer is hyperechoic and represents the serosa [15].

Inflammatory bowel disease is manifested on ultrasound as abnormal bowel wall thickening, defined as greater than 3mm, and loss of definition of the discrete bowel wall layers. Both UC and Crohn's disease result in bowel wall thickening. However, in UC the bowel wall layers are preserved, as opposed to Crohn's disease; this distinction though may not be sufficiently accurate to differentiate the two diseases by US alone. Intra-mural edema appears as generalized hypoechogenicity within the bowel wall. Conversely, fibrostenoic disease exhibits hyperechogenicity of the submucosal layer. Superficial ulcers may be detected as hypoechoic interruptions within the innermost bowel wall layer.

Doppler ultrasound can provide useful adjunct data to the structural information from conventional ultrasound. Normal bowel wall, as well as fibrostenotic bowel wall, does not usually demonstrate detectable Doppler blood flow. Therefore, the presence of intramural blood flow is suggestive of the hyperemia of active disease.

6. Nuclear medicine/Molecular imaging

As molecule-targeted therapies become increasingly prevalent in the treatment of IBD, it is likely that imaging their downstream effects directly via molecular imaging techniques will play a pivotal role in the management of patients with IBD. Molecular imaging with radionuclides in IBD has been thoroughly investigated. Analogous to conventional fluoroscopy, planar scintigraphic imaging was the predominant method of nuclear imaging for IBD in the past, but recently tomographic techniques such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) have supplanted this two-dimensional modality. As novel, targeted imaging agents become clinically available, it is reasonable to expect that molecular imaging will be critical in directly tracking the efficacy of therapies in patients with IBD in a manner that far precedes anatomic changes detectable by conventional imaging methods.

The pathophysiology of IBD involves infiltration of gut mucosa with activated lymphocytes and macrophages. By radiolabeling autologous white blood cells (WBCs) and re-injecting the cells into the patient, non-invasive imaging of WBC migration into areas of inflamma-

tion can be achieved. The radionuclide Tc-99m has been used in such a paradigm to label WBCs, and Tc-99m-labeled WBCs have been thoroughly investigated as a highly sensitive and specific instrument for diagnosing IBD. Radiolabeled WBCs may also be helpful to prognosticate response to therapy within only a few days of its initiation [16, 17].

Beyond WBCs, multiple radio-labeled probes targeting inflammation have been studied, including interleukins such as IL-2 and IL-8. Additionally, Annexin V, a molecular probe specific for apoptosis, has been shown to function as an early marker of response to therapy in patients with IBD being treated with infliximab.

The advent of positron-emitting radionuclides has paved the way for the introduction of PET imaging into clinical practice, a modality that enjoys far greater spatial resolution than single photon techniques. The most widely used PET imaging agent is 2-deoxy-2[^{18}F]fluoro-d-glucose (FDG), a radiolabeled glucose molecule that accumulates in areas of increased glycolysis. Imaging with FDG-PET has a reported sensitivity and specificity for colonic mucosal inflammation on par with endoscopy.

With the recent introduction of whole-body PET-MRI scanners, combined PET imaging with MR enterography offers the benefits of MRI morphological assessment of diseased areas with PET quantitation of inflammatory activity. The exquisite soft tissue differentiation of MRI coupled with the molecular sensitivity of PET has the potential to provide unparalleled structure-function correlation. The simultaneous acquisition of the two data sets that can be performed with new hybrid PET-MRI systems allows for true co-registration of PET and MR images (Figure 8); this feature is particularly relevant for abdominal imaging, as peristalsis can result in significant changes in bowel positioning.

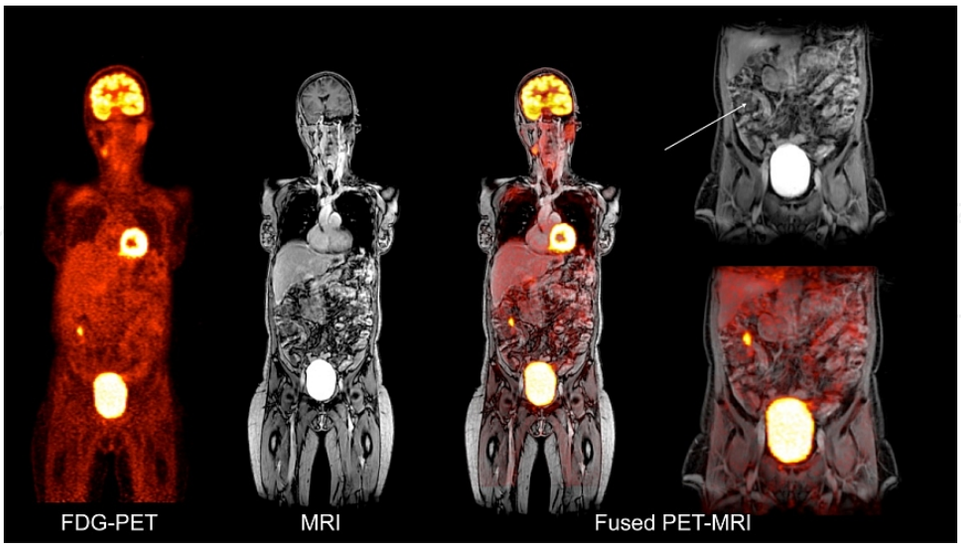

Figure 8. PET-MRI of patient with cecal inflammation. Fused imaging demonstrates small area of active inflammatory changes in the cecum that would be difficult to diagnose on either FDG-PET or MR imaging independently. Images generously provided by Drs. Alex Guimaraes, Ciprian Catana, Bruce Rosen, and David Berger (Massachusetts General Hospital, Boston, MA).

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7. Special considerations in the pediatric population

Performing diagnostic imaging examinations on pediatric patients requires consideration of several important factors. For example, pediatric patients may not be able to tolerate prolonged examinations such as MR enterography, necessitating the use of sedation to obtain satisfactory images. Moreover, not only are pediatric patients with IBD committed to a lifetime of imaging studies, but also their increased percentage of actively dividing tissue and relatively smaller body habitus render them inherently more sensitive to radiation injury and mutagenesis compared an adult. When these risks are coupled with their baseline increased risk of malignancy due to IBD, the importance of radiation dose reduction becomes apparent.

The association between diagnostic radiation and cancer risk is controversial. Directly studying the effects of ionizing radiation on malignancy risk is extremely challenging. Frequently cited epidemiologic data are based on atomic bomb survivors and nuclear power plant workers who were exposed to radiation levels that exceed those in diagnostic imaging. Moreover, the deleterious effects of radiation likely have a prolonged incubation time, perhaps on the order of decades, before they are clinically apparent. A recent large retrospective study of CT scans performed on pediatric patients suggests a measurable but small increase in the risk of malignancy [18]. It should be noted that the radiation doses associated with CT scans included in that study are significantly higher than current CT technique. Nonetheless, there is little doubt that every effort should be made to reduce the radiation exposure in pediatric patients to minimize any potential risk.

Estimating the magnitude of absorbed radiation during a CT examination can be made through the use of phantoms. Though no patient, and especially no pediatric patient, is identical to the standard, adult-sized body phantom, this approach remains the most quantitative means of estimating radiation levels within the body during a CT exam. However, extrapolating malignancy risk from these data is difficult, as different organs exhibit unique susceptibilities to radiation exposure. For example, the gonads are far more radio-sensitive than muscle tissue. For this reason, the concept of "effective dose" was introduced. This term, measured in millisieverts (mSv), reflects an attempt to create a standard metric that quantifies the impact of the absorbed radiation [19]. Effective dose is calculated by multiplying the absorbed radiation dose by a conversion factor for the body segment that was imaged; this conversion factor varies based upon the radiosensitivity of the exposed organs.

The choice of imaging modality for IBD over the past two decades has trended towards an increase in the use of CT. Pediatric patients may undergo multiple CT examinations over their lifetime, and the cumulative effective dose they receive may exceed 75 mSv, a level beyond which radiation-induced malignancy is felt to become an increasing concern. Patients with Crohn's disease are imaged far more frequently than those with UC. Also, patients who require immunosuppressive therapy or surgery are also at a higher risk of frequent imaging. Additional risk factors include stricturing or penetrating disease [20].

The most important avenue for reducing radiation dose is the eradication of unnecessary examinations. Minimizing exposure time during fluoroscopy should be standard practice.

Multiple techniques for reducing radiation dose in CT examinations have been developed and should be implemented when imaging pediatric patients. Finally, substituting non-ionizing radiation imaging modalities such as MRI and ultrasound should be considered when appropriate.

8. Conclusions and recommendations

The modalities described in this chapter each demonstrate their own unique set of advantageous and disadvantageous features. While fluoroscopy may show superficial mucosal disease better than any cross-sectional technique, extra-luminal disease is poorly visualized. The high spatial and temporal resolution of CT has driven its rise in popularity over the past two decades; however, this examination requires the use of ionizing radiation, and an appreciation of the possible associated risks is paramount prior to selecting this modality. While MRI is more costly and time consuming, it may be the best choice in a clinical situation where minimizing radiation dose is important or when soft tissue characterization is required.

For imaging symptomatic patients with suspected IBD, we recommend fluoroscopic upper GI and small bowel series because of its high sensitivity for early IBD as well as its accuracy for diagnosing other disease entities (e.g. sprue, infectious enteritides) that can mimic IBD. For initial imaging evaluation of newly diagnosed Crohn's disease, as well as evaluation of symptomatic exacerbation of known Crohn's disease in adult patients, CT enterography is recommended because of its superior ability to detect active bowel inflammation as well as extraluminal and extraintestinal disease manifestations. Urgent and emergent complications such as abscess formation and acute bowel obstruction are best imaged with traditional CT using intravenous and no enteric contrast. Crohn's disease patients with perianal symptoms should be investigated with pelvic MRI. MR enteroraphy is becoming the preferred primary imaging modality for pediatric patients, as well as adult patients who previously have undergone multiple prior CT exams, because of its lack of ionizing radiation. In patients with longstanding IBD with persistent obstructive symptoms, MR enterography is the best imaging modality for distinguishing inflammatory from fibrotic stricture [21], which has important therapeutic implications. Enteroclysis techniques should generally be reserved for those patients with remitting-relapsing obstructive symptoms despite normal enterography studies, as a provocative examination to detect short strictures. There is likely to be an increasing role for ultrasound in surveillance imaging in the future given its low cost and lack of requirement of sedation or oral contrast preparation.

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Author details

Rahul A. Sheth and Michael S. Gee

Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

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